REVIEW

Перспективы использования лазерной допплеровской флоуметрии в оценке кожной микроциркуляции крови при сахарном диабете

© Д.А. Куликов[1], А.А. Глазков[1], Ю.А. Ковалева[1], Н.В. Балашова[1], А.В. Куликов[2]

[1]ГБУЗ МО Московский областной научно-исследовательский клинический институт им. М.Ф. Владимирского, Москва
[2]ФГБУН Институт теоретической и экспериментальной биофизики РАН, Пущино

В обзоре рассматриваются научные и клинические аспекты применения лазерной допплеровской флоуметрии (ЛДФ) в изучении и диагностике состояния микроциркуляторного русла при сахарном диабете (СД). ЛДФ является неинвазивным количественным методом оценки микроциркуляции, его возможности включают анализ микроциркуляторных ритмов и проведение функциональных проб с различными видами провокационных воздействий, что позволяет исследовать состояние регуляторных механизмов микроциркуляции.
Использование ЛДФ в научных исследованиях позволило выявить характерные для СД изменения функционирования микроциркуляторного русла. Результаты части работ позволяют говорить о том, что микроциркуляторные нарушения не только являются патогенетическим звеном развития осложнений, но и наблюдаются у пациентов с ранними нарушениями углеводного обмена и могут предшествовать манифестации диабета. Однако метод до сих пор не получил распространения в клинической практике. В обзоре проанализированы факторы, ограничивающие внедрение ЛДФ в практическую медицину, предложены пути повышения ее клинической значимости.
Ключевые слова: *сахарный диабет; микроциркуляция; лазерная допплеровская флоуметрия; неинвазивная диагностика*

Prospects of Laser Doppler flowmetry application in assessment of skin microcirculation in diabetes

© Dmitry A. Kulikov[1], Alexey A. Glazkov[1], Yulia A. Kovaleva[1], Natalia V. Balashova[1], Alexander V. Kulikov[2]

[1]Moscow Regional Research and Clinical Institute (MONIKI), Moscow, Russia
[2]Institute of Theoretical and Experimental Biophysics of Russian Academy of Sciences, Pushchino, Russia

This review includes results of scientific and clinical use of laser Doppler flowmetry (LDF) in patients with diabetes mellitus. LDF is a non-invasive method for the quantitative evaluation of microcirculation, which can assess microcirculatory rhythms and conduct functional tests with various impacts, allowing the exploration of regulatory mechanisms of microcirculation.
LDF reveals specific diabetes changes in the regulatory function of microcirculation. Microcirculation disturbances, which are traditionally associated with the pathogenesis of complications, also occur in patients with early disorders of carbohydrate metabolism and may precede the manifestation of diabetes. However, this method is still not applied in clinical practice. In this review, we analysed factors limiting the implementation of LDF in practical medicine and suggest ways to improve its clinical significance.
Keywords: *diabetes mellitus; microcirculation; laser Doppler flowmetry; non-invasive diagnostics*

CC BY-NC-SA 4.0

Diabetes mellitus (DM) is a group of metabolic diseases characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycaemia in patients with diabetes is associated with damage and dysfunction in various organs, including the eyes, kidneys, nerves, heart and blood vessels [1]. According to the International Diabetes Federation of 2015, an estimated 415 million people suffer from DM globally (one out of every 11 adults). By 2040, this number is expected to reach 642 million (one out of every 10 adults) [2].

Due to the high prevalence of complications, DM is one of the most common causes of disability and mortality among the working age population [2]. Systemic microvascular disorders play an important role in the pathogenesis of diabetic complications. They lead to microangiopathy and neuropathy through the development of primary lesions in vessels that ensure blood supply to the peripheral nervous system [3,4]. Impaired neural regulation of vascular tone in the microcirculatory bed, macroangiopathy and renal injuries trigger further microcirculatory network damage, establishing a vicious circle of diabetic complications.

© Russian Association of Endocrinologists, 2017
Received: 26.07.2016. Accepted: 06.06.2017.
Сахарный диабет. 2017;20(4):279-285 doi: 10.14341/DM8014 Diabetes Mellitus. 2017;20(4):279-285

Ocular fundus examination by an ophthalmologist is a routine diagnostic procedure for evaluating microcirculation status. However, this procedure is subjective and unsuitable for early diagnosis, because it reveals microcirculatory disorders after the onset of complications [5]. Thus, the procedure does not allow adequate assessment of microcirculation for more effective disease control.

Alternatively, microcirculation status can be evaluated through measurements in the skin, which is the most accessible organ for such a procedure [6,7]. Multiple techniques for assessing skin microcirculation are currently available: videocapillaroscopy, optical coherence tomography, laser Doppler imaging etc. [8,9]. Laser Doppler flowmetry (LDF) deserves particular attention given its capacity for non-invasive testing with various functional effects. Moreover, its relatively low cost and ease of use have sparked much interest within the scientific community.

LASER DOPPLER FLOWMETRY

LDF was first used for the assessment of blood microcirculation in 1972 wherein Riva et al. measured retinal perfusion in a rabbit [10,11]. Nonetheless, not until the 1980s had the method been first applied in medical practice. In 1982, Tenland et al. placed significant effort into adapting the method for measuring skin microcirculation [12]. Furthermore, in 1985, Swiontkowski et al. used LDF for estimating bone marrow perfusion [13].

Non-invasiveness is one of the most important characteristics that make LDF highly valuable for diagnostics [8]. The principle behind the method lies in the laser probing of tissues, measurement of reflected signals and analysis of the Doppler frequency shift of the light scattered by the red blood cells. The depth of the tissue analysed is usually around 1 mm (for wavelengths ranging from green to infrared, the thickness can be between 0.5 and 2 mm). Depending on the type of tissue tested, it can contain arterioles, terminal arterioles, capillaries, postcapillary venules, venules and arteriolo-venular anastomoses [14].

LDF allows the non-invasive measurement of microcirculation at various sites, including the skin and mucosa. Ultimately, LDF is intended to analyse perfusion, which is measured in relative or perfusion units (PU) and is directly proportional to the number of erythrocytes and their average speed. The simplest way to assess microcirculation with LDF is to measure baseline perfusion [14,15]. Real-time registration of perfusion is performed using a special device that eventually creates a perfusion versus time graph, also called an LDF-gram. Routine analysis of the LDF-gram implies calculation of the mean value, standard deviation and coefficient of variation of perfusion over a period of time [16].

The microcirculatory bed is a complex system constantly regulated through changes in vascular diameter (vasomotions) [14]. The wavelet transform of an LDF-gram allows the analysis of the amplitude–frequency characteristics of these vasomotions. The oscillation frequency in the vessels is believed to lie within certain limits depending on the origin of these oscillations. Endothelial oscillations have the lowest frequency (0.0095–0.02 Hz), followed by neurogenic (0.021–0.046 Hz), myogenic (0.047–0.145 Hz), respiratory (0.2–0.4 Hz) and cardiac (0.8–1.6 Hz) oscillations [16,17].

Besides measuring baseline perfusion, various functional tests can be applied to estimate skin microcirculation using the LDF technique. These tests can increase the informativeness of the examination by assessing regulatory mechanisms using external stimuli. The occlusion test is one of the most frequently used functional tests [9,18]. It involves temporary occlusion of microcirculation (by raising the sphygmomanometer cuff pressure to suprasystolic values) in the upper or lower extremities with subsequent registration of post-occlusive reactive hyperaemia. The duration of the occlusion may vary between 1 and 5 min, whereas pressure may vary between a value 40 mmHg higher than the systolic pressure and 300 mmHg [9,19,20]. Data analysis methods may also vary: analysing maximum, mean and relative values of post-occlusive hyperaemia; calculating the area under the graph; etc. [21,22]. Despite the large number of studies that have used the occlusion test, comparison of their results is complicated because of the lack of measurement standardisation.

Other frequently used tests include temperature, respiratory and pharmacological tests. However, their procedures vary significantly in different studies [8,9,23]. Pharmacological tests are the most valuable methods for assessing endothelium-dependent and endothelium-independent vasodilation. These tests are usually performed through iontophoresis using acetylcholine or sodium nitroprusside as a pharmacological agent [24–27]. During pharmacological tests, multiple factors can affect the effectiveness of iontophoresis and, therefore, the examination results. These include the duration of the procedure, pH and concentration of the solution; type of solvent, skin thickness and electrical resistance; density and activity of sebaceous and sweat glands and some others [9,25,28].

Thus, LDF is a non-invasive method that enables quantitative evaluation of the microcirculatory network, as well as the assessment of different regulatory mechanisms using functional tests. Such advantages have made LDF one of the most common methods for assessing microcirculation [9,29]. A significant proportion of publications devoted to LDF have involved microcirculation assessment in patients with DM, arterial hypertension, burns and conditions characterised by impaired blood rheology/haemostasis [30–33].

Despite the large number of studies in this area, comparison of their results and implementation into clinical practice have been complicated by several methodological and metrological factors, including the lack of measurement standardisation, methods for data registration and constructive differences in devices used for measurement [24,34].

USE OF LDF FOR THE ASSESSMENT OF MICROCIRCULATION IN PATIENTS WITH DM

DM is one of many diseases wherein the use of LDF for scientific and/or clinical purposes is potentially beneficial considering its ability for estimating multiple parameters. Assessment of microcirculation for early diagnosis of DM and its complications, as well as for monitoring treatment efficacy, appears to be very promising [35,36,37].

However, as already mentioned, existing methodological and metrological factors often create substantial difficulties in standardising currently available data.

Controversial results obtained after comparing baseline microcirculation values in patients with DM and healthy controls suggest low informativeness of baseline perfusion assessment [33]. Some authors report decreased baseline microcirculation in patients with DM compared with those in controls [38], whereas others find no significant differences [39] or a trend towards increased baseline microcirculation in patients with DM [40].

Many researchers have ventured into studying microcirculation rhythms. Tigno et al. studied microcirculation in rhesus macaques with different stages of DM and showed that vasomotions become less chaotic with the progression of DM [41]. This can be explained by the impaired homeostatic function of the microcirculatory network and the loss of possible rapid responses to environmental changes [42]. Using an experimental model of insulin resistance (Wistar rats), Newman et al. demonstrated that insulin interacts directly with the receptors of smooth muscle cells (including sphincters) in terminal arterioles that regulate blood flow through the capillary bed. Insulin infusion led to an increase in 0.1 Hz oscillations, which is considered to be part of the myogenic rhythm [43].

We should stress that changes in skin vasomotions are observed in people with insulin resistance even before manifestations of DM [44]. These changes are associated with an impaired neurogenic vasodilatory mechanism resulting from nociceptive non-myelinated C-fibre damage, which causes decreased vasodilatory response to heating [45]. This analysis can be potentially useful for the early diagnosis of polyneuropathy [46]. LDF was shown to be informative in studies evaluating skin microcirculation in patients with type 1 DM, given that it helped to reveal decreased neurogenic rhythms in the forearm [47].

The disadvantages of LDF analysis include its high sensitivity to changes in experimental conditions (room temperature and patient's movements), long duration of perfusion registration (30–40 min) and the need for special data processing software, which also requires a highly qualified operator [42].

LDF can also be used to evaluate endothelial function, which is usually assessed via the occlusion test [48,49]. Endothelial dysfunction leads to impaired NO synthesis, resulting in decreased post-occlusive reactive hyperaemia, which is used as an indicator of blood flow reserves [21,22]. Pharmacological and temperature tests can also be used to assess endothelial function in patients with DM [50]. In such cases, endothelial dysfunction manifests as a decrease in vasodilatory response to stimuli.

Temperature tests cover a large number of regulatory mechanisms. Temperature-induced vasodilation was shown to involve both endothelium and axonal reflexes [23]. Assessment of several microcirculation regulatory mechanisms and possible changes therein using a single test increases the probability of detecting statistically significant differences in the microcirculation of patients with DM [50,51].

The use of LDF to identify early stage microcirculation disorders accompanying the development of insulin resistance and preceding type 2 DM looks very promising [36,37]. Experimental studies on animals showed that microcirculatory changes in muscle tissues can lead to insulin resistance [52]. Frisbee et al. (2007) demonstrated a correlation between obesity, microcirculatory rarefaction and reduced nitric oxide bioavailability [53,54]. LDF allows the detection of microcirculatory changes in patients with obesity but without DM [55].

On the basis of the results of multiple studies, LDF has been shown to detect specific microcirculatory changes in patients with DM, such as impaired endothelial function and neural regulation of vascular tone. LDF has also been able to determine specific microcirculation features in people with early stage glucose metabolism disorders who are at high risk for DM. Despite its non-invasive nature, ease of use and promising results from multiple studies, the LDF method is not widespread in medical practice. One possible reason is that it has been associated with low test informativeness for a single patient, given that microcirculation assessment does not help physicians make a clinical decision.

One of the major disadvantages of LDF is the high variability of parameters measured (and, therefore, the low reproducibility of the results), which allows ambiguous conclusions on the microcirculation status of a single patient and limits its use in clinical practice [9]. Another problem is related to the differentiation between normal and abnormal values, which are very close in patients with DM. LDF works perfectly when comparing patient groups within research studies. However, it becomes almost useless when making conclusions regarding the microcirculatory status after a single examination. The use of LDF in routine clinical practice is limited to cases wherein patients have significant changes in LDF parameters, which would allow easy detection because of the nature of the disease (burns and vibration disease) [36,37,57].

Statistical significance (and statistical power of a study) is often achieved by increasing the sample size and not the magnitude of the differences. Let us consider a hypothetical example of a research that compares two groups of people (20 in each). Let us also suppose that the mean perfusion value in groups 1 and 2 is 6.1 ± 1 and 7.1 ± 1 PU, respectively. Using the two-tailed Student's t-test, the p-value is determined to be 0.0032, which indicates a significant difference. Moreover, adding 30, 40 or 50 participants in each group further increases the level of statistical significance. However, the p-value does

not reflect the practical significance of the study results. Plotting the distribution function for these groups (Fig. 1) reveals that their area of overlap is too large (over 60%) to be of use for diagnostic purposes.

Unfortunately, majority of the published manuscripts have similar problems [56]. There are two approaches in reducing the area of overlap: decreasing the dispersion (scatter) and increasing the differences (distances) between them. This can be achieved by the following measures:

- use of functional tests (in particular, tests with combined effects) and
- additional mathematical processing of the results (for example, moving to 'relative values') and calculation of diagnostic ratios.

The first approach is used in the majority of the articles cited in this review. However, single tests are not always sufficient to achieve diagnostic significance. Moreover, the lack of standardised techniques for these tests, as already mentioned, creates additional problems.

The second approach increases the sensitivity of the method. For example, Hsiu et al. managed to find statistically significant differences using entropy analysis [58]. The present article could also be an example, considering that we managed to increase the level of significance by converting microcirculation into relative values and applying an original algorithm for data processing [59]. The combination of these approaches enhances the diagnostic value of LDF, which may probably help in the implementation of this purely scientific method into routine clinical practice.

CONCLUSION

LDF is an easy-to-use, non-invasive method for real-time quantitative assessment of microcirculation. It has been widely used in multiple research studies and could be potentially useful in routine clinical practice. LDF has demonstrated its effectiveness in detecting microcirculatory changes in patients with DM by providing valuable information regarding endothelial dysfunction, neuropathy, early stage microcirculatory disorders associated with insulin resistance, assessment of treatment efficacy etc.

Unfortunately, LDF is currently used in research studies only. Its implementation into routine clinical practice is restrained by several methodological and metrological factors, including high variability of measured parameters, lack of standard algorithms for testing and problems with data processing.

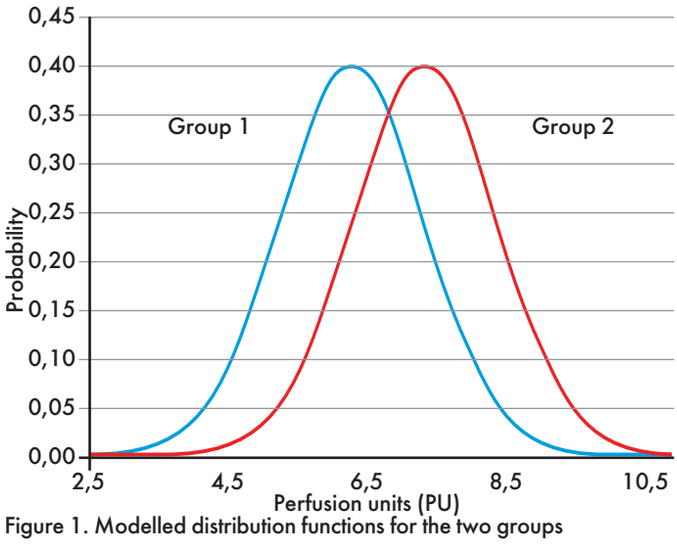

Figure 1. Modelled distribution functions for the two groups

For LDF to be implemented into practical medicine, it should provide clinicians with valuable information that would be helpful in making clinical decisions. In addition to group statistics, researchers should analyse clinical information on the disease course and outcome and develop diagnostic models for a single patient. This can be achieved through pathophysiologically reasonable functional tests (including combined tests), standardisation of measurement methods and implementation of various mathematical algorithms for data processing.

ADDITIONAL INFORMATION

FUNDING

The study was funded by the Moscow Regional Research and Clinical Institute named after M.F. Vladimirsky.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this manuscript.

AUTHORS' CONTRIBUTION

Kulikov D.A. planned the review, analysed publications and drafted the manuscript (Background and 'Use of LDF for the assessment of microcirculation in patients with DM'); Glazkov A.A. searched and analysed publications and drafted the manuscript ('Laser Doppler flowmetry'); Kovaleva Yu.A. analysed the data related to clinical use of the method and drafted the manuscript ('Use of LDF for the assessment of microcirculation in patients with DM'); Balashova N.V. drafted the manuscript (Background) and compiled the list of references; Kulikov A.V. edited the manuscript.

Список литературы | References

1. Смирнов А.Н. Элементы эндокринной регуляции. – М.: ГЭОТАР-Медиа; 2006. – 352 с. [Smirnov AN. *Elementy endokrinnoy regulyatsii*. Moscow: GEOTAR-Media; 2006. 352 p. (in Russ.)]
2. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation; 2015. Available from: http://www.diabetesatlas.org.
3. Reaven GM. Role of insulin resistance in human disease. *Nutrition*. 1997;13(1):64-65. doi: 10.1016/s0899-9007(96)00380-2
4. Дедов И.И., Мельниченко Г.А., Фадеев В.Ф. Эндокринология. – М.: ГЭОТАР-Медиа, 2007. – 432 с. [Dedov I I, Mel'nichenko GA, Fadeev VF. *Endokrinologiya*. – Moscow: GEOTAR-Media, 2007. 432 p. (in Russ.)]
5. Verma A, Raman R, Vaitheeswaran K, et al. Does neuronal damage precede vascular damage in subjects with type 2 diabetes mellitus and having no clinical diabetic retinopathy? *Ophthalmic research*. 2012;47(4):202-207. doi: 10.1159/000333220
6. Nilsson GE, Tenland T, Ake Oberg P. Laser-Doppler methods for the assessment of microcirculatory blood flow. *Transactions of the Institute of Measurement and Control*. 1982;4(2):109–112. doi: 10.1177/014233128200400206
7. Holowatz LA, Thompson-Torgerson CS, Kenney WL. The human cutaneous circulation as a model of generalized microvascular function. *Journal of Applied Physiology*. 2008;105(1):370–372. doi: 10.1152/japplphysiol.00858.2007.
8. Wright C, Kroner C, Draijer R. Non-invasive methods and stimuli for evaluating the skin's microcirculation. *Journal of pharmacological and toxicological methods*. 2006;54(1):1-25. doi: 10.1016/j.vascn.2005.09.004
9. Roustit M, Cracowski JL. Noninvasive assessment of skin microvascular function in humans: an insight into methods. *Microcirculation*. 2012;19(1):47-64. doi: 10.1111/j.1549-8719.2011.00129.x
10. Riva C, Ross B, Benedek GB. Laser Doppler measurements of blood flow in capillary tubes and retinal arteries. *Invest Ophthalmol*. 1972;11(11):936-944.
11. Swiontkowski MF. Laser Doppler Flowmetry—Development and Clinical Application. *The Iowa orthopaedic journal*. 1991;11:119.
12. Nilsson GE, Tenland T, Oberg PA. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Transactions on Biomedical Engineering*. 1980;(10):597-604. doi: 10.1109/tbme.1980.326582
13. Swiontkowski M, Tepic S, Ganz R, Perren S. Laser Doppler flowmetry for measurement of femoral head blood flow. Experimental investigation and clinical application. *Helv Chir Acta*. 1986;53(1-2):55.
14. Крупаткин А.И., Сидоров В.В. Лазерная допплеровская флоуметрия микроциркуляции крови. – М: Медицина; 2005. – 254 с. [Krupatkin AI, Sidorov VV. *Lazernaya dopplerovskaya floumetriya mikrotsirkulyatsii krovi*. Moscow: Meditsina; 2005. 254 p. (in Russ.)]
15. Almond N. Laser *Doppler flowmetry: theory and practice*. In: Belcaro G, Hoffman U, Bollinger A, Nicolaides A, editors. *Laser Doppler*. London: Med-Orion; 1994. p. 17-31.
16. Крупаткин А.И., Сидоров В.В. Функциональная диагностика состояния микроциркуляторно-тканевых систем: колебания, информация, нелинейность: руководство для врачей. – М.: Книжный дом "ЛИБРОКОМ"; 2013. – 496 с. [Krupatkin AI, Sidorov VV. *Funktsional'naya diagnostika sostoyaniya mikrotsirkulyatorno-tkanevykh sistem: kolebaniya, informatsiya, nelineynost': rukovodstvo dly avrachey*. – Moscow: Knizhnyy dom "LIBROKOM", 2013. 496 p. (in Russ.)]
17. Stefanovska A, Bračič M, Kvernmo HD. Wavelet analysis of oscillations in the peripheral blood circulation measured by laser Doppler technique. *IEEE Transactions on Biomedical Engineering*. 1999;46(10):1230-1239. doi: 10.1109/10.790500
18. Bircher A, Boer EM, Agner T, et al. Guidelines for measurement of cutaneous blood flow by laser Doppler flowmetry. *Contact dermatitis*. 1994;30(2):65-72. doi: 10.1111/j.1600-0536.1994.tb00565.x
19. Ninet J, Fronek A. Cutaneous postocclusive reactive hyperemia monitored by laser Doppler flux metering and skin temperature. *Microvascular research*. 1985;30(1):125-132. doi: 10.1016/0026-2862(85)90044-5
20. Wilkin JK. Periodic cutaneous blood flow during postocclusive reactive hyperemia. *American Journal of Physiology-Heart and Circulatory Physiology*. 1986;250(5):H765-H768
21. Yvonne-Tee GB, Rasool AHG, Halim AS, Rahman ARA. Reproducibility of different laser Doppler fluximetry parameters of postocclusive reactive hyperemia in human forearm skin. *Journal of pharmacological and toxicological methods*. 2005;52(2):286-292. doi: 10.1016/j.vascn.2004.11.003
22. Stiefel P, Moreno-Luna R, Vallejo-Vaz AJ, et al. Which parameter is better to define endothelial dysfunction in a test of postocclusive hyperemia measured by laser-Doppler flowmetry? *Coronary artery disease*. 2012;23(1):57-61. doi: 10.1097/MCA.0b013e32834e4f34
23. Cracowski JL, Roustit M. Current methods to assess human cutaneous blood flow. An updated focus on laser based-techniques. Microcirculation. 2016;23(5):337-344. doi: 10.1111/micc.12257
24. Turner J, Belch JJ, Khan F. Current concepts in assessment of microvascular endothelial function using laser Doppler imaging and iontophoresis. *Trends in cardiovascular medicine*. 2008;18(4):109-116. doi: 10.1016/j.tcm.2008.02.001
25. Ramsay JE, Ferrell WR, Greer IA, Sattar N. Factors critical to iontophoretic assessment of vascular reactivity: implications for clinical studies of endothelial dysfunction. *Journal of cardiovascular pharmacology*. 2002;39(1):9-17. doi: 10.1097/00005344-200201000-00002
26. De Caterina R. Endothelial dysfunctions: common denominators in vascular disease. *Current opinion in lipidology*. 2000;11(1):9-23. doi: 10.1097/00041433-200002000-00003
27. Kellogg DL, Jr., Zhao JL, Wu Y. Endothelial nitric oxide synthase control mechanisms in the cutaneous vasculature of humans in vivo. *American journal of physiology Heart and circulatory physiology*. 2008;295(1):H123-H129. doi: 10.1152/ajpheart.00082.2008
28. Ferrell WR, Ramsay JE, Brooks N, et al. Elimination of electrically induced iontophoretic artefacts: implications for non-invasive assessment of peripheral microvascular function. *Journal of vascular research*. 2002;39(5):447-455. doi: 10.1159/000064515
29. Shepherd AP, Öberg PA. *Laser-Doppler blood flowmetry*. Springer Science & Business Media; 1990. 396 p.
30. Khatib M, Jabir S, Fitzgerald O'Connor E, Philp B. A systematic review of the evaluation of laser Doppler techniques in burn depth assessment. *Plast Surg Int*. 2014;2014:1-13. doi: 10.1155/2014/621792.
31. Galbois A, Bigé N, Pichereau C, Boëlle PY, et al. Exploration of skin perfusion in cirrhotic patients with septic shock. *Journal of hepatology*. 2015;62(3):549-555. doi: 10.1016/j.jhep.2014.10.012.
32. Van Sloten TT, Czernichow S, Houben AJ, et al. Association between arterial stiffness and skin microvascular function in individuals without and with type 2 diabetes: Combined report of The SUVIMAX2 study and the maastricht study. *Am J Hypertens*. 2015;28(7):868-876. doi: 10.1093/ajh/hpu246
33. Fredriksson I, Larsson M, Nystrom FH, et al. Reduced arteriovenous shunting capacity after local heating and redistribution of baseline skin blood flow in type 2 diabetes assessed with velocity-resolved quantitative laser Doppler flowmetry. *Diabetes*. 2010;59(7):1578-1584. doi: 10.2337/db10-0080
34. Obeid A, Barnett N, Dougherty G, Ward G. A critical review of laser Doppler flowmetry. *Journal of medical engineering & technology*. 1990;14(5):178-181. doi: 10.3109/03091909009009955
35. Franklin VL, Khan F, Kennedy G, et al. Intensive insulin therapy improves endothelial function and microvascular reactivity in young people with type 1 diabetes. *Diabetologia*. 2008;51(2):353-360. doi: 10.1007/s00125-007-0870-2
36. Wiernsperger N, Rapin RJ. Microvascular diseases: is a new era coming? *Cardiovascular & Hematological Agents in Medicinal Chemistry*. 2012;10(2):167-183. doi: 10.2174/187152512800388885
37. Wiernsperger NF, Bouskela E. Microcirculation in insulin resistance and diabetes: more than just a complication. *Diabetes & metabolism*. 2003;29(4):6S77-6S87. doi: 10.1016/s1262-3636(03)72791-8
38. Rendell M, Bamisedun O. Diabetic cutaneous microangiopathy. *The American journal of medicine*. 1992;93(6):611-618. doi: 10.1016/0002-9343(92)90193-f
39. Colberg SR, Parson HK, Nunnold T, et al. Effect of an 8-week resistance training program on cutaneous perfusion in type 2 diabetes. *Microvascular research*. 2006;71(2):121-127. doi: 10.1016/j.mvr.2005.11.005
40. Jorneskog G, Brismar K, Fagrell B. Pronounced skin capillary ischemia in the feet of diabetic patients with bad metabolic control. *Diabetologia*. 1998;41(4):410-415. doi: 10.1007/s001250050923
41. Tigno XT, Hansen BC, Nawang S, et al. Vasomotion becomes less random as diabetes progresses in monkeys. *Microcirculation*. 2011;18(6):429-439. doi: 10.1111/j.1549-8719.2011.00103.x
42. Au M, Rattigan S. Barriers to the management of Diabetes Mellitus–is there a future role for Laser Doppler Flowmetry? *The Australasian medical journal*. 2012;5(12):627-632. doi: 10.4066/amj.2012.1526
43. Newman J, Dwyer RM, St-Pierre P. Decreased microvascular vasomotion and myogenic response in rat skeletal muscle in association with acute insulin resistance. *The Journal of physiology*. 2009;587(11):2579-2588. doi: 10.1113/jphysiol.2009.169011
44. Vinik AI, Erbas T, Park TS, et al. Dermal neurovascular dysfunction in type 2 diabetes. *Diabetes Care*. 2001;24(8):1468-1475. doi: 10.2337/diacare.24.8.1468
45. Stansberry KB, Peppard HR, Babyak LM. Primary nociceptive afferents mediate the blood flow dysfunction in non-glabrous (hairy) skin of type 2 diabetes: a new model for the pathogenesis of microvascular dysfunction. *Diabetes Care*. 1999;22(9):1549-1554. doi: 10.2337/diacare.22.9.1549

46. Aso Y, Inukai T, Takemura Y. Evaluation of skin vasomotor reflexes in response to deep inspiration in diabetic patients by laser Doppler flowmetry. A new approach to the diagnosis of diabetic peripheral autonomic neuropathy. *Diabetes Care*. 1997;20(8):1324-1328. doi: 10.2337/diacare.20.8.1324
47. Bernardi L, Rossi M, Leuzzi S, et al. Reduction of 0.1 Hz microcirculatory fluctuations as evidence of sympathetic dysfunction in insulin-dependent diabetes. *Cardiovascular research*. 1997;34(1):185-191. doi: 10.1016/s0008-6363(97)00017-5
48. Герасимчук П.А., Кисиль П.В., Власенко В.Г., Павлышин А.В. Показатели эндотелиальной дисфункции у больных с синдромом диабетической стопы // Вестник Российской академии медицинских наук. – 2014. – Т. 69. – № 5-6. – С. 107-110. [Gerasymchuk PA, Kisil PV, Vlasenko VG, Pavlyshyn AV. Endothelial Dysfunction Indicators in Patients with Diabetic Foot Syndrome. *Annals of the Russian academy of medical sciences*. 2014;69(5-6):107-110. (in Russ.)] doi: 10.15690/vramn.v69i5-6.1053
49. Стаценко М.Е., Деревянченко М.В. Возможности коррекции дисфункции эндотелия на фоне комбинированной антигипертензивной терапии у больных артериальной гипертонией с сахарным диабетом 2-го типа // Кардиология. – 2015. – Т. 55 – №3. – С. 17-22. [Statsenko ME, Derevyanchenko MV. Possibilities of Correction of Endothelial Dysfunction at the Background of Combined Antihypertensive Therapy in Patients With Arterial Hypertension and Type 2 Diabetes. *Kardioilogia*. 2015;55(3):17-22. (in Russ.)] doi: 10.18565/cardio.2015.3.17-20
50. Heimhalt-El Hamriti M, Schreiver C, et al. Impaired skin microcirculation in paediatric patients with type 1 diabetes mellitus. *Cardiovascular diabetology*. 2013;12:115. doi: 10.1186/1475-2840-12-115
51. Jan YK, Shen S, Foreman RD, Ennis WJ. Skin blood flow response to locally applied mechanical and thermal stresses in the diabetic foot. *Microvascular research*. 2013;89:40-46. doi: 10.1016/j.mvr.2013.05.004
52. Clark MG. Impaired microvascular perfusion: a consequence of vascular dysfunction and a potential cause of insulin resistance in muscle. *American journal of physiology – Endocrinology and metabolism*. 2008;295(4):E732-E750. doi: 10.1152/ajpendo.90477.2008
53. Frisbee JC. Reduced nitric oxide bioavailability contributes to skeletal muscle microvessel rarefaction in the metabolic syndrome. *American journal of physiology – Regulatory, integrative and comparative physiology*. 2005;289(2):R307-R316. doi: 10.1152/ajpregu.00114.2005
54. Frisbee JC. Obesity, insulin resistance, and microvessel density. *Microcirculation*. 2007;14(4-5):289-298. doi: 10.1080/10739680701282945
55. Czernichow S, Greenfield JR, Galan P, et al. Microvascular dysfunction in healthy insulin-sensitive overweight individuals. *Journal of hypertension*. 2010;28(2):325-332. doi: 10.1097/HJH.0b013e328333d1fc
56. Лапитан Д.Г., Рогаткин Д.А. Функциональные исследования системы микроциркуляции крови методом лазерной доплеровской флоуметрии в клинической медицине: проблемы и перспективы // Альманах клинической медицины. – 2016. – Т. 69 – №44-2. – С. 249-259. [Lapitan DG, Rogatkin DA. Functional studies on blood microcirculation system with laser dopplerflowmetry in clinical medicine: problems and prospects. *Almanac of Clinical Medicine*. 2016;69(44-2):249-259. (in Russ.)] doi: 10.18786/2072-0505-2016-44-2-249-259.
57. Maga P, Henry BM, Kmiotek EK, et al. Postocclusive Hyperemia Measured with Laser Doppler Flowmetry and Transcutaneous Oxygen Tension in the Diagnosis of Primary Raynaud's Phenomenon: A Prospective, Controlled Study. *BioMed Research International*. 2016;2016:1-9. doi: 10.1155/2016/9645705.
58. Hsiu H, Hsu CL, Hu HF, et al. Complexity analysis of beat-to-beat skin-surface laser-Doppler signals in diabetic subjects. *Microvascular research*. 2014;93:9-13. doi: 10.1016/j.mvr.2014.02.009
59. Глазков А.А., Куликов Д.А., Древаль А.В., и др. Разработка способа диагностики нарушений микроциркуляции крови у больных сахарным диабетом методом лазерной допплеровской флоуметрии // Альманах клинической медицины. – 2014. – Т. 31 – №1. – С. 7-10. [Glazkov A.A., Kulikov D.A., Dreval, et al. Development of non-invasive method for blood microcirculation disorders diagnostics in diabetic patients using laser doppler flowmetry. *Almanac of Clinical Medicine*. 2014;31(1):7-10. (in Russ.)] doi: 10.18786/2072-0505-2014-31-7-10.

Информация об авторах [Authors Info]

Глазков Алексей Андреевич [**Alexey A. Glazkov**, MD]; адрес: 129110, Москва, ул. Щепкина, 61/2, к. 8 [address: 61/2/8 Shchepkin st., Moscow, 129110 Russian Federation]; ORCID: https://orcid.org/0000-0001-6122-0638; eLibrary SPIN: 3250-1882; e-mail: staaglz@gmail.com.
Куликов Дмитрий Александрович, к.м.н. [Dmitry A. Kulikov, MD, PhD]; ORCID: http://orcid.org/0000-0002-4273-8295; eLibrary SPIN: 1980-2229; e-mail: d.kulikov@monikiweb.ru. Ковалева Юлия Александровна, к.м.н. [Yulia A. Kovaleva, MD, PhD]; ORCID: http://orcid.org/0000-0001-7327-2486; eLibrary SPIN: 3250-1882; e-mail: yulia.kovaleva@mail.ru. Балашова Наталья Валерьевна, к.б.н. [Natalya V. Balashova, MD, PhD in Biology]; ORCID: http://orcid.org/0000-0002-0548-3414; eLibrary SPIN: 2355-6837; e-mail: balashovan77@mail.ru. Куликов Александр Владимирович, д.б.н. [Alexander V. Kulikov, PhD in Biology]; ORCID: http://orcid.org/0000-0003-1434-0615; eLibrary SPIN: 1762-1441; e-mail: 29.04.55@mail.ru.

Цитировать:

Куликов Д.А., Глазков А.А., Ковалева Ю.А., Балашова Н.В., Куликов А.В. Перспективы использования лазерной допплеровской флоуметрии в оценке кожной микроциркуляции крови при сахарном диабете // Сахарный диабет. — 2017. — Т.20. — №4. — С. 279-285. doi: 10.14341/DM8014

To cite this article:

Kulikov DA, Glazkov AA, Kovaleva YA, Balashova NV, Kulikov AV. Prospects of Laser Doppler flowmetry application in assessment of skin microcirculation in diabetes. *Diabetes mellitus.* 2017;20(4):279-285. doi: 10.14341/DM8014